

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: OH, Kwang-wook, et al.
Serial No.: 10/783,127
Conf. No.: 2678
Filed: February 19, 2004
Title: **POLYMERASE CHAIN REACTION DEVICE AND METHOD OF
REGULATING OPENING AND CLOSING OF INLET AND OUTLET OF
THE POLYMERASE CHAIN REACTION DEVICE**
Examiner: BEISNER, William H.
Art Unit: 1797
Docket No: YPL-0082

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Advisory Action dated September 30, 2008 and in conjunction with the Notice of Appeal filed concurrently herewith, the Applicants submit the following remarks in support of the Pre-Appeal Brief Request for Review:

REMARKS

Claims 1-16 are pending in the present Application. Claims 3 – 5, 7 – 14 and 16 have been withdrawn and no claims have been cancelled, leaving Claims 1, 2, 6 and 15 for consideration upon entry of the present Amendment. Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, 6 and 15 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent No. 6,875,619 to Blackburn in view of US 2002/0054835 to Robotti, et al. (“Robotti”). (Office Action dated 08-06-2008, page 3) Applicants respectfully traverse this rejection.

In making the rejection, the Examiner has stated that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ thermoreversible gels in a system of the primary reference for the known and expected result of providing an alternative means recognized in the art to achieve the same result, control of the flow

of fluids with a microfluidic device, and for advantages discussed by the reference of Robotti.” (Office Action dated 08-06-2008, page 4)

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; that the prior art relied upon, or knowledge generally available in the art at the time of the invention, must provide some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combined references. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988) The obviousness inquiry also requires consideration of common knowledge and common sense. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006) (“Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense.”)

Claim 1 is directed to a PCR (polymerase chain reaction) device comprising an inlet through which a biochemical fluid is injected; an outlet through which the biochemical fluid is discharged; a PCR channel positioned between the inlet and the outlet; first and second micro-valves, which control opening and closing of the inlet and the outlet; and a sol-gel transformable material, which transforms from a sol state into a gel state at a temperature lower than DNA denaturation temperature, annealing temperature and extension temperature and higher than room temperature; the sol-gel material transformable material being positioned in the first and second micro-valves; the sol-gel material being operative to control the opening and closing of the first and second micro-valves.

Blackburn is directed to a variety of microfluidic devices with configurations that include the use of biochannels or microchannels comprising arrays of capture binding ligands to capture target analytes in samples. (see Abstract) As the Examiner contends, Blackburn discloses a PCR device that includes an inlet; an outlet; a PCR channel (22); a first microvalve (32); and a second microvalve (34). (Office Action dated 08-06-2008, page 4) Blackburn does not teach a valve having a gel that can reversibly change its state to permit the valves to open and close.

Robotti teaches micro-fluid devices and methods for their uses. (see Abstract) Robotti teaches that the device comprises at least one micro-valve comprising a phase reversible material e.g., a reversible gel that reversibly changes its state in response to an applied stimulus, e.g., a thermoreversible gel. (see Abstract) Robotti lists methyl cellulose as a gel material. (see paragraph [0033])

One of ordinary skill in the art would not have combined Blackburn with Robotti because they teach away from each other. In particular, the channels sizes disclosed by Robotti are much larger than those disclosed by Blackburn. One of ordinary skill in the art noting these disparate teachings between Robotti and Blackburn would not have combined references in the manner made by the Examiner. If the valves disclosed by Robotti were included in the device of Blackburn it would militate against the teachings of Blackburn. In addition, if the valves of Robotti were to be included in the device of Blackburn, there would be massive discontinuities in walls of the microfluid channels prescribed by Blackburn. Blackburn does not desire this.

In the manufacturing of the device Blackburn teaches that:

The lamination process involves the application of pressure to the stacked layers. For

example, in the conventional lamination process, a uniaxial pressure of about 1000 to 1500 psi is applied to the stacked green-sheet layers that is then followed by an application of an isostatic pressure of about 3000 to 5000 psi for about 10 to 15 minutes at an elevated temperature, such as 70° C. Adhesives do not need to be applied to bind the green-sheet layers together when the conventional lamination process is used.

However, pressures less than 2500 psi are preferable in order to achieve good control over the dimensions of such structures as internal or external cavities and channels. Even lower pressures are more desirable to allow the formation of larger structures, such as cavities and channels. For example, if a lamination pressure of 2500 psi is used, the size of well-formed internal cavities and channels is typically limited to no larger than roughly 20 microns. Accordingly, pressures less than 1000 psi are more preferred, as such pressures generally enable structures having sizes greater than about 100 microns to be formed with some measure of dimensional control. Pressures of less than 300 psi are even more preferred, as such pressures typically allow structures with sizes greater than 250 microns to be formed with some degree of dimensional control. Pressures less than 100 psi, which are referred to herein as "near-zero pressures," are most preferred, because at such pressures few limits exist on the size of internal and external cavities and channels that can be formed in the multilayered structure.

(Col. 19, lines 38 – 65) While Blackburn teaches that various pressures may be used to manufacture a device with different channel sizes, it desires dimensional control of the surfaces of the microchannel. Blackburn further states that:

The microfluidic channels of the present invention are channels generally less than 200 microns in plastic with molding or embossing technology. The channels need to be of the dimension to support pumping of the microfluidic system. The microfluidic channel may have any shape, for example, it may be linear, serpentine, arc shaped and the like. The cross-sectional dimension of the channel may be square, rectangular, semicircular, circular, etc. There may be multiple and interconnected microchannels with valves to provide for recirculation.

(Col. 23, lines 49 – 59)

Blackburn also teaches that:

That is, "mesoscale" as used herein refers to chambers and microchannels that have cross-sectional dimensions on the order of 0.1 μm to 500 μm . The mesoscale flow channels and wells have preferred depths on the order of 0.1 μm to 100 μm , typically 2-50 μm . The channels have preferred widths on the order of 2.0 to 500 μm , more preferably 3-100 μm .

(Col. 25, line 63 – Col. 26, line 7) While Blackburn teaches that pressure can be varied to produce different sized channels, it also teaches that the maximum dimension for a microfluidic channel is 500 micrometers (see Col. 26, line 4) and that the maximum cross-sectional area is 100 micrometers X 500 micrometers = 50,000 square micrometers. (see Col. 26, lines 4 – 7) The maximum cross-sectional area of a channel as prescribed by Blackburn is therefore equal to 50,000 square micrometers, which is equal to 0.0005 square centimeters.

Robotti, on the other hand, teaches that:

Generally, the micro-fluidic devices in which the subject valves find use will have at least one micro-compartment positioned at some point in the fluid flow path, where the term "micro-compartment" means any type of structure in which micro-volumes of fluid may be contained, and includes micro-chambers, micro-channels, micro-conduits and the like. The term micro-chamber, as used herein, means any structure or compartment having a volume ranging from about 1 μ l to 500 μ l, having cross-sectional areas ranging from about 0.05 cm² with a chamber depth of 200 μ m to 5 cm² with a chamber depth of 1 mm; usually from about 10 μ l to 500 μ l, having a cross-sectional area ranging from about 0.5 cm² with a chamber depth of 200 μ m to about 5 cm² with a chamber depth of 1 mm; and more usually from about 20 μ l to 200 μ l having a cross-sectional area ranging from about 1 cm² with a chamber depth of 200 μ m to about 4 cm² with a chamber depth of 500 μ m.

(see paragraph [0024]) Thus the minimal cross-sectional area for the micro-chamber or micro-channel prescribed by Robotti is 0.05 square centimeters, which is at least 100 times larger than the cross-sectional area prescribed by Blackburn. This larger area prescribed by Blackburn is due to the gelatinous characteristics of the gels that activate the valves.

One of ordinary skill in the art reading these dissonant teachings of Blackburn and Robotti would not have combined references in the manner made by the Examiner. In addition, the Applicants would like to submit that because of the large difference in sizes of the microchannels prescribed by Blackburn and Robotti, one of ordinary skill in the art would not be able to use a valve prescribed by Robotti in the device of Blackburn. The use of the valve prescribed by Robotti in the device disclosed by Blackburn would lead to major discontinuities in fluid flow in the microchannels. One of ordinary skill in the art examining Blackburn and noting his statement (underlined above) that there must be dimensional control over the microchannels and that it desired mesopores (pores having diameters less than 100 micrometers) would also not want to add a significant discontinuity to accommodate the valves of Robotti, especially since Blackburn's devices require smaller dimensions for its microchannels. In addition, it is not clear whether the gel disclosed by Robotti would even be able to flow in the fine channels disclosed by Blackburn.

The Examiner has stated that the Applicants have tried to show non-obviousness by attaching the references individually. (Advisory action dated 09-30-08, page 2) This is incorrect. Case law holds that "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). To find obviousness, the Examiner must "identify a reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed new invention does." *Id.* The Examiner has cited no logical reason why one of ordinary skill in the art would combine two references that teach dimensions that vary widely from one another.

The Examiner has stated that "Applicants are comparing the channel dimensions of Blackburn with the chamber dimensions of Robotti. One can clearly see from Figure 2 of Robotti that the valves (18) are associated with the microchannels (14) rather than the microchambers (17). Paragraph [0024], last 11 lines of Robotti clearly states that the maximum dimensions of the microchannel should not exceed 250 micrometers, which is of the same order as the microchannels as Blackburn." (Advisory action dated 09-30-08, page 2) The Applicants respectfully disagree.

It is to be noted first that Robotti does not make any distinction between the microchannels and microchambers. (see the underlined portion above) While the Examiner has pointed to the Figures of Robotti as showing the valve disposed in a microchannel, Robotti's specification takes the position that the "subject valves find use in at least one micro-compartment positioned at some point in the fluid flow path, where the term "micro-compartment" means any type of structure in which micro-volumes of fluid may be contained, and includes micro-chambers, micro-channels, micro-conduits and the like". In addition, all of the Figures of Robotti show that the valve has a much larger cross-sectional area than the microchannel, thus indicating that the cross-sectional area where the gel is disposed must be significantly larger than that of the microchannel.

In addition, Robotti teaches that the microchannel is essentially present in a planar shaped substrate-a card shaped substrate, a disc shaped substrate. (see paragraph [0026]) The Figures of Robotti clearly indicate that the microchannels are disposed upon the surface of a planar device. The devices of Blackburn contain channels that are disposed internally after laminating several green sheets. While Blackburn does contend that all types of valves can be used, it would be extremely difficult for one of ordinary skill in the art to dispose a gel at a precise internal position in a microchannel or microchamber especially when the gel has to be disposed after lamination and when the microchannel is curvaceous. (See Figures 1, 6 and 7 of Blackburn) One of ordinary skill in the art noting that the gel would have to be disposed in an internal microchannel rather than on the surface would be dissuaded from combining references. These references teach away from one another and one of ordinary skill noting the disparity in the dimensions prescribed by the two references would not have sought to combine them in the manner made by the Examiner. For this reason at least, the Applicants believe that the Examiner has not made a prima facie case of obviousness over Blackburn in view of Robotti. The Applicants respectfully request a withdrawal of the obviousness rejection and an allowance of the claims.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

CANTOR COLBURN LLP

By /David E. Rodrigues/
David E. Rodrigues
Registration No. 50,604

Date: December 8, 2008